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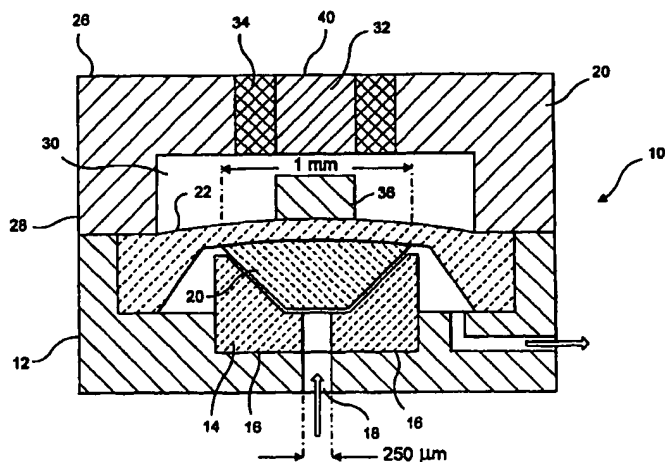
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| (51) International Patent Classification ⁶ : A61K 9/22, A61M 31/00, A61N 1/30 | A1 | (11) International Publication Number: WO 99/17749 (43) International Publication Date: 15 April 1999 (15.04.99) |
|--|-----------|--|

(21) International Application Number: PCT/US98/17867

(22) International Filing Date: 28 August 1998 (28.08.98)

(30) Priority Data:
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York, NY 10017 (US).(81) Designated States: CA, JP, European patent (AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
SE).**Published**
With international search report.

(54) Title: A MICROMACHINED VALVE FOR FLUID APPLICATIONS



(57) Abstract

A micro-valve (10) for fluid applications has been developed using the micro-fabrication technologies of bulk micro-machining, and LIGA high aspect ratio machining. Coupled with a magnetic micro-actuator (32), the operation of this micro-valve (10) has been demonstrated for the control of liquids.

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**A MICROMACHINED VALVE
FOR FLUID APPLICATIONS**

BACKGROUND OF THE INVENTION

Field of the Invention

5 The invention is related to valves and more particularly to a microvalve for handling fluid applications.

Brief Description of Related Art

10 Implantable infusion pumps hold many advantages over the oral administration of drugs or the infusion of drugs through a percutaneous access site. Some of these advantages include the ability to administer the drug in a site-specific manner which frequently involves the reduction of the necessary dose as well
15 as the alleviation of undesired side effects. Furthermore, the total implantation of the infusion device is largely successful in preventing the entrance of bacteria leading to common complications of external infusion systems and local infection.
20 The cases that require long-term, continuous drug infusion no longer require hospitalization as frequently; in most cases, the patients that receive implantable pumps have freedom of movement and can be treated as outpatients.

25 The advantages of implantable pumps are not only evident from a practical perspective, but from a pharmacological point of view as well. The advantages of continuous or modulated-continuous drug infusion avoids the problems of drug concentration in
30 the bloodstream. The inability to control the timing of the drug concentration can lead to periods of near toxic concentrations or at the other extreme, insufficient drug therapy. Moreover, the implantable pump provides the physician with a localized method
35 of drug delivery. Flexible access to a wide variety

of specific body sites creates the potential for much more versatile methods of drug delivery. Simultaneous drug introduction through two separate catheters from the same drug reservoir would be possible, as would the ability to use two different implantable systems in the same patient. The miniaturization of the drug delivery system is a powerful enabling tool for future applications for implantable drug delivery systems. The predominant implementation has been for intra-arterial infusion chemotherapy into the hepatic artery for metastases from colorectal cancer. Other uses have included intra-arterial plus intravenous infusion of drugs to treat metastatic carcinoma. Pumps have also been used to administer heparin into the central venous system for problems with clotting that cannot be treated by conventional oral anticoagulants. Delivery of morphine into the spinal spaces for the treatment of pain caused by malignancy has been effective using implantable systems. Implantable pumps have also been approved by the FDA (Food and Drug Administration) to deliver localized infusions of chemotherapeutic drugs for various solid tumors. These uses of an implantable system are just a few of the drug delivery applications that have benefited from the development of implantable systems. In some of these cases, particularly, uses where infusion occurs directly into the cerebral area or the intrathecal space, a totally implantable system is the only practical method, due to the high risk of infection from a percutaneous access site.

There are several implantable pumps for drug delivery on the market today. Two of these pumps are the Infusaid Implantable Infusion System manufactured

by Pfizer Infusaid in Norwood, MA., and is the SynchroMed pump manufactured by Medtronic, Inc. of Minneapolis, MN. Both of these pumps are similar in size to the dimensions of a hockey puck. The
5 SynchroMed pump delivers a drug by using a peristaltic mechanism. Rollers sequentially compress an elastic tube that connects the drug reservoir with the delivery catheter. The peristaltic motion moves the fluid through the catheter. The Infusaid pump
10 utilizes a positive pressure chamber that constantly pushes against the drug reservoir. Solenoid activated outlet valves release the drug into the catheter.

These pumps and others on the market can easily
15 be used for a set flow rate. Furthermore, some systems can be programmed to follow a rudimentary schedule of infusion to follow the circadian rhythms of the body. However, in many applications, the drug therapy would be much more effective if the flow rate
20 were variably controlled. The most effective pumping system would be closed loop in nature, with delivery control based on a sensor input. For example, insulin therapy would require implementation with a reliable glucose sensor to be ultimately effective.

25 The most obvious weakness in the Infusaid, SynchroMed and other pumps is the size of the device. Admittedly, the precursor to these implantable pumps was a pump on a shoulder strap linked through a percutaneous site to the body. The "hockey puck"
30 size was a marked improvement to early ambulatory pumps. However, the size of the Infusaid and similar models of pumps limits its implantation site to the peritoneal cavity or a few other sites, but always subcutaneously on the muscle fascia. It is then
35 necessary to thread a catheter to the delivery site.

Through the use of Micro Electro Mechanical Systems (MEMS) technology, the goal is to create a microvalve for a much smaller drug delivery system that will create more flexible methods of implementing the
5 implantable pump for drug therapy. In addition to the benefits of reducing size, MEMS devices are able to be easily coupled with control electronics without the complications in packaging that may exist with the current pumping systems.

10 Over the last few decades, the well characterized techniques of integrated circuit fabrication have been applied to creating novel, free-standing microstructures. Processes of photolithography, isotropic, anisotropic, and
15 plasma etching, thin-film deposition, and fusion bonding are processes that are widely used within the field of semiconductor device research. These processes have been thoroughly studied and in many cases, comprehensive models have been generated to
20 predict the effects of these processes. This well characterized fabrication technology has been applied to the development of Micro Electro Mechanical Systems (MEMS). MEMS is actually a very broad term referring to microstructures, both sensors and
25 actuators, created using a variety of processing techniques. The earliest MEMS devices were created in the 1960's and resulted from the development of solid-state pressure and acceleration transducers. These devices were fabricated using anisotropic
30 etching of silicon wafers, that is, etching along certain crystallographic planes at a higher rate than other planes. This type of etching is called bulk micromachining and will be discussed in more detail in the following. Since MEMS processing technology
35 is so closely linked in origin and practice with

integrated circuit fabrication techniques, the integration of electronics with these movable structures is logical. A typical microelectromechanical system would have sensors and
5 actuators linked in a closed-loop configuration controlled by on-board electronics.

Bulk micromachining has been mentioned as one of the main fabrication techniques used to create MEMS devices. There are two other mainstream techniques
10 that are currently in widespread use. The first technique is surface micromachining. In this process, layers of metal, polysilicon, or nitride are deposited on the surface of a silicon wafer or a similar substrate. The layers are deposited and
15 patterned using conventional UV photolithography. Typical thicknesses for the layers are 0.5 to 3.0 μm . Surface micromachining is relatively simple to do in a conventional clean room and is effective at creating low aspect ratio (thickness to width)
20 structures. With the use of a bottom sacrificial layer, usually silicon dioxide, structures that are simultaneously anchored to the substrate in one area and suspended in another can be produced. This technique has been used to create linear comb
25 actuators, thin gears, micromanipulators, and other devices.

The second mainstream MEMS technique is LIGA processing. LIGA was developed in Germany and is a German acronym that stands for Lithographie
30 Galvanoformung, and Abformung or lithography, electroplating, and injection molding. More recently in the United States, LIGA processing has been further developed at the University of Wisconsin in Madison. The major difference between LIGA and the
35 other types of micromachining (surface and bulk), is

that LIGA creates high aspect ratio microstructures. This technique utilizes the ability to electroplate metallic films through thick X-ray lithographically defined molds on a supporting substrate. The

5 resulting structures can have aspect ratios approaching 50:1. The first step of this process, deep X-ray lithography (DXRL), uses proximity printing with high energy X-rays from a synchrotron light source. The resist used to create these high

10 aspect ratio micro-structures is typically polymethylmethacrylate (PMMA), which is bonded to a handler wafer. The short wavelengths of the X-rays, on the order of 10 angstroms, enables the creation of thick structures with very well defined and tight

15 tolerances to the mask pattern. The thickness of the PMMA determines the final thickness of the LIGA structures. After the PMMA is exposed to the high energy X-rays, the exposed PMMA is developed away, which leaves a thick plastic structure bonded to the

20 handler wafer. At this time, if a seed layer of metal was deposited prior to the PMMA bonding, the PMMA structure can be used as a mold within which metal can be electroplated to the top surface of the PMMA. Following the electroplating, the PMMA can be

25 completely removed which leaves a metal structure that can be used as a form for injection molding. Rotary micromotors, gear trains, and a variety of other structures have been fabricated using this technology.

30 The present invention primarily uses a modified LIGA process for fabricated components, coupled with bulk micromachined parts to form a microvalve useful for a drug delivery system.

SUMMARY OF THE INVENTION

The invention comprises a micromachined valve adapted by size and configuration to be implantable within the body of a mammal, including a human, which

5 comprises;

a valve housing, enclosing a valve head, a valve seat and fluid channels controlled by the cooperation of the valve head with the valve seat;

10 a valve seat within the valve housing, said seat having

- (i) a fluid inlet end;
- (ii) a fluid outlet end; and
- (iii) sidewalls tapering from the fluid outlet to the fluid inlet;

15 a movable valve head mounted in the housing, having a valve face adapted by size and configuration to mate with the valve seat and seal the valve closed;

20 said valve head being movable from a first position wherein the valve face is in sealed closure with the valve seat, to a second position wherein the valve face is not in sealed closure with the valve seat; and

25 magnetic means attached to the valve head for moving the valve head from the first position to the second position.

The micromachined valve of the invention may be used to precisely control the delivery of small amounts of liquid medications in an implanted drug
30 delivery system. Micromachining produces a microvalve. A microvalve is a flow control device for gas or liquid flow rates ranging from tens of microliters to milliliters per minute. Microvalves are typically fabricated using micromachining
35 techniques from the integrated circuit industry that

result in devices with dimensions on the orders of microns to tens of millimeters with very tight geometric tolerances.

The microvalve is suitable for high or low liquid
5 flow rates. For example, the application in an insulin pump has a targeted flow rate of 1 ml-3ml per day. This application would make use of Humulin, Eli Lilly and Co.'s synthesized insulin, which can be highly concentrated, or some other similar insulin.
10 The application of hypertension therapy utilizes drugs that include Inderal and Tenormin. Both of these drugs are classified as beta blockers and are usually given in doses with an upper limit of 30 μ l per day. This would be a low flow rate application
15 as opposed to the relatively high flow rate of the insulin pump application.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a cross-sectional side view of an embodiment microvalve of the invention.

20 Figure 2 is a diagrammatic overview of the conventional LIGA process (Prior Art).

Figure 3 illustrates the present process steps for wafer scale assembly.

25 Figure 4 is a cross-sectional view of a tapered valve seat and valve head of the invention.

Figure 5 is a schematic plan for a "smart implant" of the invention wherein the microvalve embodiment of Fig.1 is the basis of an implanted pharmaceutical delivery system.

30 Figure 6 is a functional schematic drawing of an implanted closed-loop micro-delivery (pharmaceutical) system employing the microvalve of Fig.1.

Figure 7 is a view as in Fig.6, but rotated 90 degrees.

Figure 8 is a top view of the implanted device of Figs.6 and 7.

Figures 9 and 10 are enlarged views of the check valve employed for the entry port of the implanted device of Figs.6-8. Fig.9 is a side view and Fig.10 is a top view.

Figure 11 is a cross-sectional side view of a microvalve of the invention incorporated in an extrocorporeal drug delivery system.

10 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

Those skilled in the art will gain an appreciation of the invention from a reading of the following description of preferred embodiments, when viewed with the accompanying drawings of Figures 1-11, inclusive.

Referring first to Figure 1, a cross-sectional side view of an embodiment microvalve 10 of the invention, it is seen that the valve 10 comprises two parts. The base 12 is a flow channel piece manufactured with conventional machining from a pre-cast PMMA sheet with a nominal thickness of about 1 to 2 mm. The channel piece base 12 is designed to accept an LIGA fabricated valve seat 14 into insets 16 in the top surface. In the center of the two insets 16 the flow channel 18 was drilled to a diameter of about 250 μm . The insets 16 were designed to be 100 μm and provide a means for mechanical alignment of the valve seat 14. In assembly, the two most common methods of alignment are optical and mechanical. Optical alignment is performed with alignment marks and a microscope. Mechanical alignment uses either structures such as pins and orifices which fit together when the bond partners are in the desired position or are aligned

at their edges. The accuracy of both methods depends on the precision of the manufacturing process. Optical alignment can be performed with a camera inspecting the sample on a computer controlled stage.

5 However, in the absence of such equipment, mechanical alignment is practical and easier, especially when done manually.

The insets 16 on the flow channel pieces base 12 feature a run out in the corners (not shown in Figure 10 1). Using conventional machining, it is almost impossible to achieve a sharp corner of the insets 16. The inset 16 is machined using an end mill, therefore, the corners will always have a radius. However, the valve seat 14 pieces are diced and the 15 corners on those pieces are sharp. The run out accommodates the corners by moving the end mill past the edge of the inset 16 in the X and Y directions. In effect, this creates small lobes in each corner. The mechanical alignment is accomplished with the 20 faces of the inset 16 and the valve seat 14, not the corners. This method of alignment is completely acceptable and effective. With stochastic vibratory methods, the valve seats 14 could be assembled into the insets 16. A typical vibratory assembly method 25 would have the flow channel pieces base 12 affixed to a table with controlled vibration. A lot of valve seats 14 can be deposited on the upper surface of the flow channel pieces base 12. With the proper frequency of vibration and the depth and size of the 30 inset 16 the flow channel pieces base 12 will fall into place.

The valve seat 14 and channel piece base 12 are bonded together using a solvent bonding method. At these sizes, the capillary effect is quite strong. 35 Instead of having to apply an even coating to one

piece and then manipulate that piece into place manually, the valve seats 14 can be positioned in the insets 16 prior to adhesive application. Applying a drop of solvent to the edge of the interface is sufficient for the capillary effect to wick the solvent across the valve seat/channel piece interface evenly with complete coverage. The bonding process is especially simplified because the bond partners are made of common material.

10 The assembly of the PMMA head 20 to the silicon membrane 22 is also straightforward. Using an assembled valve seat 14 and channel piece base 12 sub assembly as a jig, the placement of the head 20 is achieved with mechanical alignment. A small amount of very low viscosity adhesive is applied to the bottom side of the membrane 22 in the general area of the head 20 location. The gluing jig is mounted in a deep inset in a larger fixture that accepts the membrane 22 as well. The deep inset mechanically aligns the membrane 22 and channel piece base 12 so that the membrane 22 and head 20 are bonded. The membrane 22 can be removed from the gluing fixture and flipped over so that the PMMA head 20 is protruding upward. Very slight pressure can be applied to head 20 to further aid the bond between the PMMA head 20 and the silicon membrane 22.

 The Si membrane 22 implemented with the PMMA head 20 is not permanently bonded to the valve seat 14 sub assembly. Instead, the test fixture is designed such that the periphery of the membrane 22 is clamped to the periphery of the flow channel piece base 12 without compromising the elasticity of the membrane 22 itself. Advantageously, the Si membrane 22 has a thickness of about 10 μm . The preferred membrane 22 will have an elasticity such that the

membrane 22 exhibits a deflection under pressure as follows:

SI MEMBRANE THICKNESS 10 μ m DEFLECTION [mm]

| | @ 0.5 PSI | @ 1 PSI | @ 3 PSI | @ 7 PSI |
|---|-----------|---------|---------|---------|
| 5 | 0.021 | 0.030 | 0.047 | 0.067 |

The valve head 20 is designed to seal along the membrane 22 and the top of the valve seat 14. In order for this interface to be a tight seal, the primary condition is:

$$10 \quad e = V - I$$

wherein e is the etch depth of the silicon. V is the thickness of the LIGA valve seat 14 wafer and I is the depth of the inset 16 in that channel piece base 12. The head 20 thickness should be equal to V.

15 Nominally, the silicon wafer thickness is about 400 μ m; therefore, if the selected membrane 22 thickness is 10 μ m, then the etch depth would equal about 390 μ m. Following the condition stated in the above Equation, for a valve seat 14
20 thickness of 500 μ m, the inset 16 depth should be 110 μ m.

The microvalve of the invention is normally closed and this feature is primarily dependent on the stiffness of the membrane 22. If the desired
25 application for the microvalve requires a closed state at a higher pressure, the membrane 22 can be pre-biased in a downward closed state in a number of ways. The first method involves the deposition of a thin layer of nickel or some other metal of tensile
30 stress on the backside of the membrane 22. This metal would force the membrane 22 in a downward curvature which would press against the valve seat 14 with more force than the unmodified membrane 22. The other method, which involves the manipulation of the
35 membrane 22 component thicknesses, would be to create

a more shallow inset 16 that would leave the valve seat 14 protruding a little higher. For example, if the inset 16 were reduced to 100 μm , the 500 μm valve seat 14 would protrude above the top surface of base 12 a distance of 400 μm instead of 390 μm . Since the membrane 22 etch depth is 390 μm , assembling the membrane 22 to the valve seat 14 and clamping the outer periphery of the two components would result in an unpowered deflection of 10 μm . This amount of pre-bias results in a stronger normally closed implementation. The latter method of pre-biasing is simpler and less expensive to implement. Of course, if the pre-bias distance is set too high, the available displacement distance is decreased before the membrane 22 reaches the point of rupture.

Once the LIGA, bulk micromachining, and conventional machining processes are completed, the multiple component thicknesses are preferably approximately as follows:

| | | |
|----|------------------------------------|--------------------|
| 20 | <u>NOMINAL COMPONENT THICKNESS</u> | |
| | Si wafer thickness B | 400 μm |
| | Si membrane 22 thickness t | 10 μm |
| | Si etch depth e | 390 μm |
| | PMMA Vlv. seat thickness V | 500 μm |
| 25 | Channel piece thickness H | 1000 μm |
| | Inset 16 Depth I | 100 μm |

The valve seat 14 pieces may be fabricated from commercial PMMA with a nominal thickness of about 500 μm .

30 In a preferred embodiment of the invention, the valve seat 14 is tapered to meet the need for increased flow characteristics through the open valve without requiring impossible membrane 22 deflections. The modified LIGA process was applied to fabricate 35 this feature.

As shown in Figure 1, the upper part 26 of microvalve 10 comprises a magnetic steel actuator housing 28 mounted on the membrane 22 to enclose in chamber 30 the valve actuator mechanism.

5 The purpose of the actuator for the microvalve 10 is to generate enough force to displace the sealing membrane 22 upwards so that flow may occur over the valve seat 14. Therefore, the actuator will be used to attract a movable piece rather than to
10 displace it. This characteristic is important for the normally closed implementation of the valve.

There are various magnetic actuators reported in the literature for MEMS devices. Most of these devices have integrated coils created by surface
15 micromachining or some form thereof. As a result, the number of turns and the resultant generated forces are reduced. The main design goal for the actuator for microvalve 10 was to provide sufficient force to displace the silicon membrane 22. As
20 calculated, typical forces generated by integrated coils are on the order of 0.5 to 1 mN generated by a 17 turn coil operating at 300 mA. Since the force generated is directly proportional to the number of turns, and considering the difficulties of increasing
25 the number of turns with an integrated actuator, an external micro magnetic actuator 32 was designed.

The design of the actuator 32 is basic. A flat faced armature type of magnetic actuator is miniaturized and the components conventionally
30 machined. The actuator 32 follows the design principles for a macro electromagnet. With a current applied to the coil 34, flux lines are generated which attract the magnetic material bonded to the backside of the valve membrane 22. The
35 actuator 32 operates more efficiently if the housing

28 is used as a magnetic return. When the membrane 22 is displaced upwards, the magnetic material 36 on the membrane 22 is pulled against the coil 34/core 40, completing the magnetic circuit. The magnetic material 36 on the membrane 22 is soft magnetic material; however, if permanent magnetic material is used, the actuator 32 would operate in both directions. Reversing the polarity of the current would result in the repulsion of the membrane 22. This feature could be used in closing the membrane 22 against fully developed flow, if desired.

The core 40 may be threaded at the opposite end of the coil 34, providing a means of adjusting the height of the coil 34 above the membrane 22. The gap between the membrane 22 and the magnetic material 36 should be approximately 100 to 500 μm . At this distance, sufficient force is generated.

Two sizes of wire are wound on the magnetic core 40: 46 gauge and 50 gauge wire. The 46 ga. wire has a resistance of 4.207 Ω /ft and a conductor diameter of 40 μm . The 50 ga. wire has a resistance of 10.58 Ω /ft and a conductor diameter of 25 μm . Insulation adds 1-2 μm to the overall diameter of the wire. The coils are wound with approximately 1500-2000 turns per core. The coil 34 winding process is well known and was developed and performed at the Oak Ridge National Laboratories in Oak Ridge, TN. The magnetic core 40 is held in place with a pin vise and the wires wound by hand around the core 40 to form the coil 34. For more precise placement of the coil 34 windings and a more efficient implementation of the coil 34, commercial precision coil winding machines can be acquired. The 46 ga. wire coils are more robust. The coil 34 was measured to have a resistance of 80 Ω .

The placement of the magnetic material 36 on the membrane 22 is done by hand.

The valve head 20 and valve seat 14 may be fabricated by a modified LIGA process.

5 LIGA is a process of deep X-ray lithography that provides great flexibility in material choices. In order to fabricate the parts of the microvalve of the invention, the conventional LIGA was modified significantly and applied in a manner to achieve the
10 novel aspects of the microvalve 10. In order to understand the modifications that were made a clear discernment of the LIGA process is helpful.

Deep X-ray lithography and its companion LIGA process, electroplating were first demonstrated by
15 researchers at the Karlsruhe Research Center (KFK) in the early 1960's. The motivation for developing this process was an attempt to create separation nozzles for the separation of uranium isotopes. These nozzles would work more effectively if the size of
20 the separation elements was reduced to dimensions of a few micrometers. This original process consisted of three steps: deep-etch lithography, electroforming and plastic molding. The steps of a typical LIGA process is depicted in Figure 2 of the accompanying
25 drawing.

The first step, deep X-ray lithography, involves the exposure of thick photoresist layers, up to 1000 micrometers, to the high energy synchrotron radiation produced by an electron storage ring. The radiation
30 properties include high collimation and large absorption length into polymethyl methacrylate (PMMA), which is commonly used as the thick resist material. Using an appropriate mask, two-dimensionally defined patterns are transferred to
35 the PMMA without run out. The lateral tolerances of

the mask pattern compared to the resulting LIGA part are usually less than $0.1\text{ }\mu\text{m}$ per $100\text{ }\mu\text{m}$ of PMMA thickness.

The substrate for the basic LIGA process is typically a silicon wafer, since this material is easily obtainable and well suited to clean room equipment and processes of development and metal deposition. A suitable plating base layer with adequate adhesion to the substrate wafer is critical and the wafer material must not interfere with the plating process. Besides silicon wafers, glass or metal wafers can typically be used. Typical plating base material for a nickel electroplating process would be sputtered chromium or titanium followed by a layer of sputtered nickel. One variant of the LIGA process, SLIGA or sacrificial LIGA, uses a sacrificial layer deposited below the plating base layer. SLIGA leads to microstructures that are either flexible in areas or completely free to move.

After the plating base and/or sacrificial layer has been deposited on the silicon wafer, the PMMA must be properly affixed to the plating base layer. There are various methods of bonding the acrylic to the handler wafer. Casting and polymerizing PMMA with cross-linking to the plating base is the original German method. Other research groups have developed methods of bonding preformed PMMA sheets to a spun-on layer of PMMA; see U.S. Patent 5,378,583 incorporated herein by reference thereto. Typical resist thickness of $100\text{--}1000\text{ }\mu\text{m}$ are commonly used in LIGA processes.

A suitable X-ray mask is necessary before proceeding with the next steps of the LIGA process. The purpose of X-ray lithography in LIGA is different than X-ray lithography used in the manufacture of

conventional integrated circuits. The pattern transfer process for thick resists requires wavelengths on the order of 0.05-0.5 nm to maintain an uniform exposure depth. The X-ray spectrum that will be available for fabrication dictates the type of mask that needs to be fabricated. The valve seat 10 was fabricated using a storage ring that operates between 1.2 and 1.5 GeV electron energies with respective beam currents of 400 and 200 mA. The mask absorber must be a material with high atomic number such as electro-plated gold or etched tungsten in order to properly transfer the mask pattern to the exposed PMMA. The absorber pattern is supported by a silicon substrate membrane which is transparent to the synchrotron radiation.

The exposure process consists of placing the target PMMA/plating base/handler wafer and the X-ray mask wafer together in an exposure fixture into the X-ray lithography exposure station. Radiation is emitted at a bending magnet of the CAMD synchrotron storage ring. The beam goes through several chambers of inert gases and foil filters that filter the radiation to an optimal dosage and X-ray spectra. The final beam profile at the face of the X-ray mask is approximately 5 cm wide and 0.5 cm high. The mask/wafer holder fixture is mounted on a multi-axis scanning mechanism, so that the scanning mechanism moves up and down in the path of the radiation beam throughout the exposure period. The exposure time is calculated based on the thickness of the PMMA resist, the beam energy and current, the type of filters used, and the desired dosage at the top and bottom of the resist.

The exposure step is followed by development in a developer bath specially formulated to obtain a

high selectivity between exposed and unexposed PMMA areas.

The electroplating process builds up metal from the seed layer or plating base layer on the wafer
5 into the exposed and developed regions of the PMMA. A wide variety of metals or alloys can be electroplated at this step of the process. Nickel is the most commonly used metal in conventional LIGA processing, a choice determined by the relative
10 simplicity of plating nickel. Permalloy is also used by some researchers, especially where magnetic properties may be beneficial. The wide variety of materials that can be used in the creation of LIGA three-dimensional structures is one of the strongest
15 advantages of this technology. Besides the different types of metals that lend themselves to formation by electroplating, more material choices are available if LIGA is taken to the final step of the process, injection molding. This process has not been
20 developed to the same level of maturity as the X-ray lithography and electro-plating steps. This is primarily a result of the evolution process of this fabrication technology and the challenges of thoroughly characterizing the earlier steps in the
25 process. However, a variety of materials have been demonstrated to be moldable through LIGA processing including thermoplastics., ceramics and various resins. The molding process follows the completion of the electroplating process by removing the
30 unexposed PMMA. The resulting metal structure on the handler wafer can be used for injection molding within this metal mold. Theoretically, this injection process can be reproduced many times. Therefore, the LIGA process has been used to create
35 a master from which many molded parts can be created.

The highest source of cost in the LIGA process is the exposure step in the X-ray synchrotron ring; the electroplating step can be performed with very simple, inexpensive equipment. By utilizing the LIGA
5 part as a master mold, the cost per part drops drastically.

The microvalve of the invention does not utilize the electroplating step or the injection molding process. This simplifies the fabrication process
10 developed for fabricating the microvalve significantly and modifies the remaining steps of the LIGA process by using the exposure beams in a novel fashion to form the unique aspects of the microvalve.

In a preferred embodiment process of the present
15 invention, the base 12 of microvalve 10 is manufactured separate from upper part 26 and then assembled together to manufacture the microvalve 10.

Figure 3 shows one method of assembly at the wafer scale. Even if the total number or spacing of valve
20 seats 14 does not exactly match the spacing of the membrane 22 wafer, a partial array of valve seats 14 can be assembled. A new array of valve seats 14 can then be brought in place over the membrane 22 wafer, translated by an appropriate distance and assembled
25 to more membranes 22. The assembled valves 10 will be diced after bonding for incorporation into an appropriately packaged drug delivery system. This type of assembly can be automated for commercial production.

30 Referring now to Figure 4, there is shown a preferred configuration for the valve head 20 shown withdrawn from valve seat 14. In the preferred embodiment, valve head 20 is tapered downward in dimension from top to bottom and may, in fact, be
35 cylindrical, frusto-conical or pyramidal. The valve

seat 14 corresponds with the configuration of head 20 so that the exterior surfaces of each mate and seal together when the valve 20 is closed, interrupting flow through channel 18.

5 As mentioned above, tapered valve seat 14 is defined using a modified LIGA process. Angled sidewalls can only be created by having angled exposures where the mask and wafer are tilted with respect to the incoming X-rays. This can be achieved
10 simply by designing a mask/wafer fixture that is on a controllable tilted stage. The design process is more complex because angled walls resulting from a LIGA exposure will have the same orientation across the entire wafer. The tapered valve, as pictured in
15 Figure 4 has angled walls that oppose each other. The tapered component of the valve seat 14 presents significant challenges on both the design and fabrication levels. Since multiple exposures are used, great care must be taken in the design stage so
20 that sunsequent exposures do not degrade the edges defined by earlier exposures.

The solution to this problem of defining multiple angled walls on the same wafer is to use multiple exposures, rotating the mask and wafer at
25 multiples of 90° with simultaneous tilting of the entire fixture. It is not cost effective to create a different X-ray mask for each tilted and rotated exposure. Therefore, the single X-ray mask created for the modified process must be designed in such a
30 way that the pattern of the absorber material is functional from each point and angle of exposure. It is extremely difficult to visualize the three dimensional effects of the progressive exposure steps, therefore, the critical design step is the
35 modeling of the effects of the proposed mask pattern

on the resist. A suitable X-ray mask is necessary before the exposure process. The pattern transfer process for thick resists requires wavelengths on the order of 0.05-0.5 nm to maintain a uniform exposure
5 depth. The selection of mask materials transparent to X-rays at these wavelengths is simplified and thicker mask substrates can be used. The absorber must be a material with high atomic number such as electroplated gold or etched tungsten. The absorber
10 pattern is supported by a substrate membrane which is transparent to the synchrotron radiation.

A conventional 4 inch silicon wafer is used as a typical mask blank. The mask blank must be transparent to X-rays, have low atomic number, be
15 robust, flat and dimensionally stable. Optical transparency is a desirable, but not mandatory characteristic that aids in alignment processes between multiple levels of LIGA exposures. The plating stencil is optically defined on a nitride-
20 covered (500 angstrom) wafer. The openings in the resist structure are plated with 5 μm of gold. After the gold is defined, the wafer is etched from the backside through a window to form the mask membrane. The final thickness of the membrane is defined by the
25 level of boron doping selected for this wafer, typically 2-3 μm . The area of the membrane is 45mm x 45mm. This bulk micromachining is accomplished with the use of potassium hydroxide (KOH). LIGA designs requiring alignment, such as multilevel LIGA
30 processes, require the fabrication of X-ray masks with optically transparent windows. MCNC has developed a novel approach that places two small alignment windows or outriggers outside the area of the central X-ray exposure membrane. The novel
35 fabrication sequence involves the photolithographic

definition of the two alignment windows by slightly modifying the existing backside membrane mask. Reactive ion etching the backside nitride layer is followed by the standard frontside fabrication sequence of defining the plating stencil and the electroplating of the gold absorber. Removal of the photoresist plating stencil and the frontside plating base completes the frontside processing. The deep boron diffused region is used as an etch stop in the KOH on the backside to form three separate membrane; the central X-ray area, and the two outrigger windows. All three membrane are still optically opaque at this time. The alignment windows are modified to be optically transparent by placing the completed X-ray mask in a horizontal position with the backside facing upwards. Isotropic silicon etch solution is placed in and confined to the outrigger windows. After a brief period, the regions become transparent while maintaining structural rigidity. Different materials have been used for the absorber; gold was selected as the simplest and relatively inexpensive absorber. The thickness of the gold is dependent on the target thickness of the PMMA to be exposed. There is a maximum deposition dose allowed on the resist surface under the membrane before cracks and bubbles form. The ratio of this dose to the maximum dose allowed on the resist surface under the absorber corresponds to an effective mask contrast of 200. For example, a target PMMA thickness of 500 μm or more would require absorber thickness of the order of 10 μm . It is noteworthy to point out that gold contamination, normally an issue with the gate oxide of silicon MOS-based devices, is not an issue with LIGA devices. The wet process of

gold absorber pattern formation is a simple, relatively inexpensive, low temperature process.

The storage ring at the Center for Advanced Microstructures and Devices in Baton Rouge, LA.,
5 operates between 1.2 and 1.5 GeV electron energies with respective beam currents of 400 and 200 mA and critical energy of 1.3 and 2.5 keV. The critical wavelengths are 9.5 angstroms and 4.8 angstroms. All exposures were performed using the X-Ray
10 Lithography Micromachining (XRLM3) beamline at port No. 7B of the CAMD storage ring. Radiation is emitted at a bending magnet of the storage ring with an energy of 5 mrad. The beamline extends from the ring a distance of 10 m, terminating with a 125 μm
15 thick beryllium window. The resulting X-ray beam is 50 x 10 mm^2 at the exposure plane. The spectrum transmitted by the Be window is in the 1.5 angstroms to 6 angstroms range with an integrated power density of 415 mW/cm and 1140 mW/cm when the storage ring is
20 operating at 1.3 GeV and 1.5 GeV, respectively with a beam current of 100 mA. This range allows for effective exposure of PMMA thicknesses up to 300 μm without filtration and thicker resists with filtration. The multichamber exposure system houses
25 a number of filters that remove the lower energy or soft X-rays. The soft X-rays prevent exposure of thicker resists because they contribute only to surface dose and not the absorption length into the PMMA. Overexposure problems such as swelling or
30 degradation of the PMMA surface are associated with the accumulation of large numbers of small volatile molecular fragments produced as a result of the degradation of the polymer.

The first chamber of the CAMD exposure station
35 subsequent to the beamline serves as a radiation

filter that controls the x-ray spectra and dose delivered to the sample. This filtering is done with a variety of foils and inert gases. For the processing involving PMMA thickness of 400 μm or
5 higher, a 14 μm aluminum foil is used to harden the X-rays. Helium gas is also present in the filtering chamber.

The exposure chamber houses a microstepper driven multi-axes scanning mechanism. The vertical
10 linear positioner has a resolution of 1.5 μm and is used to scan the sample through the X-ray beam. The sample can be mounted on two 360° rotational stages with resolution of 0.001° to accommodate precise alignment and contour motions during X-ray exposures.
15 The scanning mechanism has a computer user interface which allows coordinate velocity and motion profiles of all axes.

Deep X-Ray Lithography (DXRL) has been described as a proximity printing technique. However, unlike
20 conventional photolithography where the target resist and chrome mask are in contact with each other, DXRL requires a gap between the PMMA resist and the X-ray mask. The X-ray mask is fragile, due to the very thin membrane 22 supporting the gold absorber
25 pattern. Therefore, the resist surface must not come in contact with the mask membrane 22. Typical proximity gaps of one to several hundred microns are typical. This gap does not affect the results of the X-ray exposure. Due to the short wavelength of the
30 X-ray light, the beam does not diffuse sufficiently enough to result in adverse effects.

The design of the silicon membrane 22 follows the design for the valve seat 14 out of necessity. the size of the membrane 22 is dictated by the size

of the valve seat 14. The overall width of valve seat 14 is approximately 3 mm on edge.

The membrane 22 fabrication process begins with double sided polished wafers with low pressure chemical vapor deposited (LPCVD) nitride in a furnace at about 825°. The nitride is patterned to open up the areas to be etched. The wafers are etched using a KOH etchant held at 80°C. To create membrane 22 with 10 μm thickness from an original wafer thickness of 400 μm required approximately 5 hours. The membrane 22 thickness is determined with a timed etch process that basically uses past experience with etchants to predict the appropriate amount of etching. For more precise thicknesses, it is possible to use an etch stop that uses a layer of boron doped silicon to refine the membrane 22 thickness. In this case, an etchant such as ethylene diamine pyrocatechol (EDP) would be used. These boron doped wafers are more expensive since they require pre processing to implant the boron layer.

The microvalve 10 described above has the ability of being incorporated into an implantable (in mammals, including humans) drug delivery system.

The ability to deliver drugs in small, precise doses in a small localized tissue or organ area has many applications in the medical arena, such as insulin therapy, pain control and chemotherapy. This microvalve 10 is designed to be a normally closed, low leakage valve suitable for long term implantation.

The body temperature of the normal healthy, human body is 37°C. A pump that depended on maintaining this internal temperature for proper operation would not be suitable for implantation. The operation of the system could be compromised by

a patient's body fever or hypothermic body condition. By the same token, a pump that created a high temperature environment surrounding the pump would also be unsuitable. The heating effect would not
5 only have a deleterious effect on the body tissue surrounding the pump, but any localized heating of the drug within the pump would, in many case, also reduce the stability of the pharmaceutical solution. and therefore, the effectiveness of the drug therapy.

10 Power consumption is a key factor in the proper design of an implanted drug delivery system. Besides the heating that usually accompanies high power consumption, an implantable system will achieve its power source through the use of batteries. Poor
15 management of power consumption will necessitate the frequent replacement of batteries. For an implantable system, battery changes often necessitate the surgical removal of the system and reimplantation, a process that greatly increases the
20 chances of infection or other complications. Because of the power consumption design considerations, the implementation of a normally closed microvalve becomes the dominant design characteristic. A review of existing MEMS microvalves that have been developed
25 in the past decade indicates that the majority of these experimental devices were designed to handle gases rather than fluids. Furthermore, a very small percentage of these devices utilized a normally closed implementation. It is notable that none of
30 these devices were intended for a biomedical implementation and the designers did not necessarily need to create extremely power efficient actuators. For the target drug delivery applications selected for this invention, the duty cycle for an output
35 microvalve would remain relatively short; therefore,

a normally closed microvalve 10 is appropriate. Alternatively, an application that required a constant infusion of drug with infrequent, brief interruptions in delivery would lend itself more to
5 a normally open configuration.

It is also important to note that actuation schemes that use high voltages for actuator displacement would also be inherently impractical for implantable applications. Electrostatic
10 microactuation, for example, uses a movable electrode that is drawn towards a stationary electrode by electrostatic attraction. Typical voltages that create the attractive force range from 80-200 Volts, an inappropriate range for implantable devices.

15 Considering these design factors of size, power consumption, operating temperature, flow rate, reliability and operating voltage, an initial design was formulated.

Microvalves are critical to the proper operation
20 of microfluidic handling systems. System failure is commonly caused by valve failure or unacceptable levels of valve leak-age. There are two basic classifications of microvalves: Passive, which are dependent on pressure or some other flow
25 characteristic for operation, and active, which are operated by an actuator. By being normally open, the valves under review would consume power during the off cycle of delivery. Furthermore, the bulk of the developed microvalves has been built to control the
30 flow of gases. Flow control of incompressible fluids is a more demanding task, that presents additional challenges. Some of the previously mentioned structures are too fragile to withstand the inertial effects of liquid flow.

Passive valves are, of course, very power efficient since they require no external actuation for operation. However, a pressure dependent device is greatly limiting to the patient that receives the
5 implanted system. If the patient were to use air travel or reside in a mountainous locale, the pressure differences that might result would be detrimental to proper operation of the system. Reliable, predictable, drug infusion would be
10 difficult under those circumstances. Passive valves are also especially prone to leakage since any particulates in the delivery fluid can prevent proper sealing if the particles lodge on the valve seat 14 during operation.

15 Magnetic actuation has been commonly used in macrodomain actuators as a more efficient alternative to electrostatic field actuation. This is because the larger dimensions of conventional machines allow the storage of greater energy densities with magnetic
20 fields rather than electrostatic fields. As monolithic microactuators were developed, electrostatic actuators were favored over magnetic actuators for various reasons. Among these arguments: stored energy densities are comparable on
25 micron scales, electrostatic actuators are more efficient, and magnetically driven actuators are not compatible with silicon microfabrication technology. These arguments are true under certain circumstances and operating conditions; however, when magnetic
30 actuators are examined in terms of function, they remain the best alternative for certain applications.

Magnetic actuation is effective in applications where conducting fluids are being pumped. Such fluids would disrupt the proper operation of
35 electrostatic actuators. Many biomedical and

biological fluids are conductive, which excludes the use of electrostatic actuation. Furthermore, environments that are less than pristine where particles can clog structural elements or vital machine parts remain suitable for magnetic applications. Especially applicable to this project, magnetic actuators can be easily powered by a battery supply, which makes them useful for mobile applications such as an implantable device. It is true that if a design is limited to the opening assumption of a monolithic microfabricated actuator, the aforementioned arguments can favor electrostatic application. The micron-sized gaps within the structures of electrostatically driven actuators lead to relatively high energy densities and efficiencies.

Referring now to Figure 5, a schematic drawing of a drug delivery system, implantable in a mammal, beneath the skin, including a human, comprises the microvalve 10 of the invention. Microvalve 10 is connected by a conduit catheter 50 to a pump or pressurized reservoir 52 serving as a supply source for a medication such as, for example, insulin. The microvalve 10 releases a measured dose of the insulin through catheter 56 to an output site 60 within the mammal's body. Actuation of microvalve 10 is controlled by a microcontroller 62 including a micro processor programmed to receive signal inputs from a microsensor 66 also implanted in the mammal's body. The microsensor 66 may be, for example, for sensing pre-determined levels of glucose microsensors of this type and for sensing levels of a wide variety of biological compounds may be manufactured in accordance with the teachings of U.S. Patent 5,063,081 incorporated herein in its entirety by reference thereto. The microprocessor 58 likewise

may be a known device made by IC technology for implantation. The entire system can be powered in a conventional manner with low-voltage sources and contained in an implantable housing 68.

5 The valve may be actuated with a current of 100 mA at two separate input pressures, resulting in an increase in flow from 30-40 $\mu\text{l}/\text{min}$ to 170-180 $\mu\text{l}/\text{min}$. Reservoir 52 may be periodically re-filled through a refill system 70.

10 Those skilled in the art will appreciate that many modifications may be made to the preferred embodiments described above without departing from the spirit and scope of the invention. For example, referring now to Fig.6, there is seen a cross-
15 sectional side view of an alternate embodiment implantable device of the invention. Fig.6 is a functional schematic drawing of an implanted closed-loop micro-delivery (pharmaceutical) system employing the microvalve of Fig.1.

20 Figure 7 is a view as in Fig.6, but rotated 90 degrees.

In the Figs. 6 and 7, component parts of the implantable device corresponding to the parts shown in Fig. 5 are similarly numbered. The essential
25 differences between the device of Figs. 6 and 7 differ from the plan of Fig. 5 in that a compressed air volume fills the chamber 72 as a means of pressurizing the medication chamber 52. More significantly, there is provision for two microvalves
30 10. The redundancy assures operation of the implanted device even if one of the microvalves 10 should fail for development of a plugged flow. The microprocessor 52 can be programmed to operate each microvalve 10 independently or together in tandem.

Figure 8 is a top view of the implanted device of Figs. 6 and 7, and shows further detail.

Figures 9 and 10 are enlarged views of the check valve employed for the entry port of the implanted device of Figs. 6-8. Fig. 9 is a side view and Fig. 10 is a top view.

Figure 11 is a cross-sectional side view of a microvalve of the invention incorporated in an extrocorporeal drug delivery system.

10 It is well known in the art that many medications can be delivered by use of transdermal dosimeter; see for example the U.S. patents 4,329,999; 4,595,011; and 5,396,901 which are incorporated herein by reference thereto. The
15 microvalves of the present invention may be used to control medication delivery in such devices.

One of the significant features of the patch 66, as we call the transcutaneous delivery system shown in figure 11, is that the sensor 66 is not limited to
20 detecting body conditions, but rather can also detect external environmental conditions, such as chemical or biological agents on the battlefield. To detect such agents in the blood stream or in body fluids is wholly impractical as precious seconds, which could
25 otherwise be used to prepare and protect the body, are lost. Another feature is that the constant pressure source may be provided by a stretched elastomeric membrane 76. As these devices are
30 necessary, as it would, in all probability, be less costly and more effective to apply a new patch. By mixing the medicament with an absorption-augmenting agent, medication of low molecular weight can be rapidly absorbed through the skin. To transfer
35 larger molecular weight medicaments would require

additional epidermal stimulation such as with electricity; see Wickelgren, I., "Breaking the Skin Barrier," *Popular Science*, Dec. 1996.

WHAT IS CLAIMED IS:

1. A micromachined valve adapted by size and configuration to be implantable within the body of a mammal, including a human, which comprises;

5 a valve housing, enclosing a valve head, a valve seat and fluid channels controlled by the cooperation of the valve head with the valve seat;

a valve seat within the valve housing, said seat having

- (i) a fluid inlet end;
- 10 (ii) a fluid outlet end; and
- (iii) sidewalls tapering from the fluid outlet to the fluid inlet;

a movable valve head mounted in the housing, having a valve face adapted by size and configuration
15 to mate with the valve seat and seal the valve closed;

said valve head being movable from a first position wherein the valve face is in sealed closure with the valve seat, to a second position wherein the
20 valve face is not in sealed closure with the valve seat; and

magnetic means attached to the valve head for moving the valve head from the first position to the second position.

2. The valve of claim 1 wherein the valve head and the valve seat are tapered.

3. A method of manufacturing a plurality of microvalves which comprises;

- (a) establishing a plurality of uniform valve membranes on a silicon wafer;
- 5 (b) forming a plurality of corresponding valve seat by
 - (i) providing a preformed sheet of photoresist material which can

35

- 10 be exposed to radiation to
affect its susceptibility to a
developer;
- (ii) exposing the photoresist sheet
in a pattern to radiation which
will change its susceptibility
15 to a developer;
- (iii) mechanically removing the
material of the photoresist
sheet to reduce the thickness of
the sheet to a desired
20 thickness; and
- (iv) applying a developer to the
exposed photoresist to remove
photoresist which is susceptible
to the developer;
- 25 (c) assembling the valve heads with the
valve membranes; and
- (d) assembling the valve membranes, heads
and valve seats to a magnetic
actuator.

4. A pharmaceutical delivery system
implantable in the body of a mammal, including a
human which comprises;

- 5 (a) a microvalve of claim 1 in fluid
communication with a reservoir for
a pharmaceutical to be delivered to
the mammal;
- (b) the reservoir for said
pharmaceutical;
- 10 (c) conduit means connected to the
microvalve for delivery of the
pharmaceutical within the mammal
upon release by the microvalve;

- 15 (d) a microprocessor programmed to
activate the microvalve to release the
pharmaceutical upon receiving a pre-
determined signal from a biosensor;
and
- 20 (e) a biosensor electrically connected
to the microprocessor for trans-
mitting a signal representative of
a condition within the mammal
requiring release of a dose of the
pharmaceutical.

5. The system of claim 4 for delivery of pharmaceutical insulin and the biosensor detects levels of blood sugar in the mammal.

6. The system of claim 5 wherein the signal is transmitted when a blood sugar level in the mammal exceeds about 120 mg/cc.

7. The system of claim 1 which further comprises a second microvalve of claim 1 connected to the reservoir for redundancy.

8. The system of claim 4 for transdermal delivery.

9. A system for the transdermal delivery of a pharmaceutical to a mammal, including a human, which comprises;

- 5 (a) a microvalve of claim 1 in fluid
communication with a reservoir for
a pharmaceutical to be delivered to
the mammal;
- (b) the reservoir for said
pharmaceutical;
- 10 (c) conduit means connected to the
microvalve for delivery of the

pharmaceutical to a transdermal applicator upon release by the microvalve;

- 15 (d) a microprocessor programmed to activate the microvalve to release the pharmaceutical upon receiving a pre-determined signal from a biosensor;
- 20 (e) a biosensor electrically connected to the microprocessor for transmitting a signal representative of a condition external to the mammal requiring release of a dose of the pharmaceutical; and
- 25 (f) means for attaching the system to the mammal whereby the transdermal applicator is placed in contact with the mammal's skin.

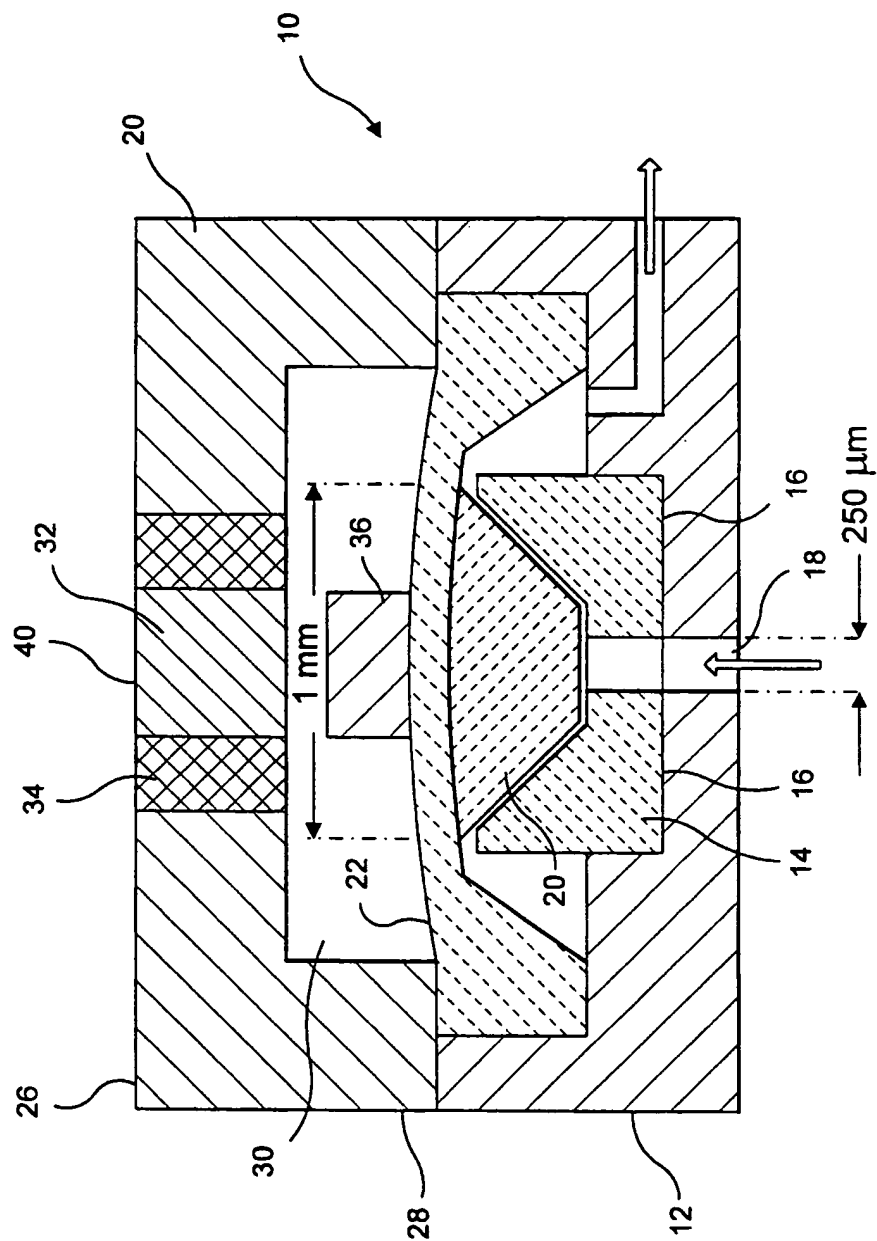


FIG. 1

2/9

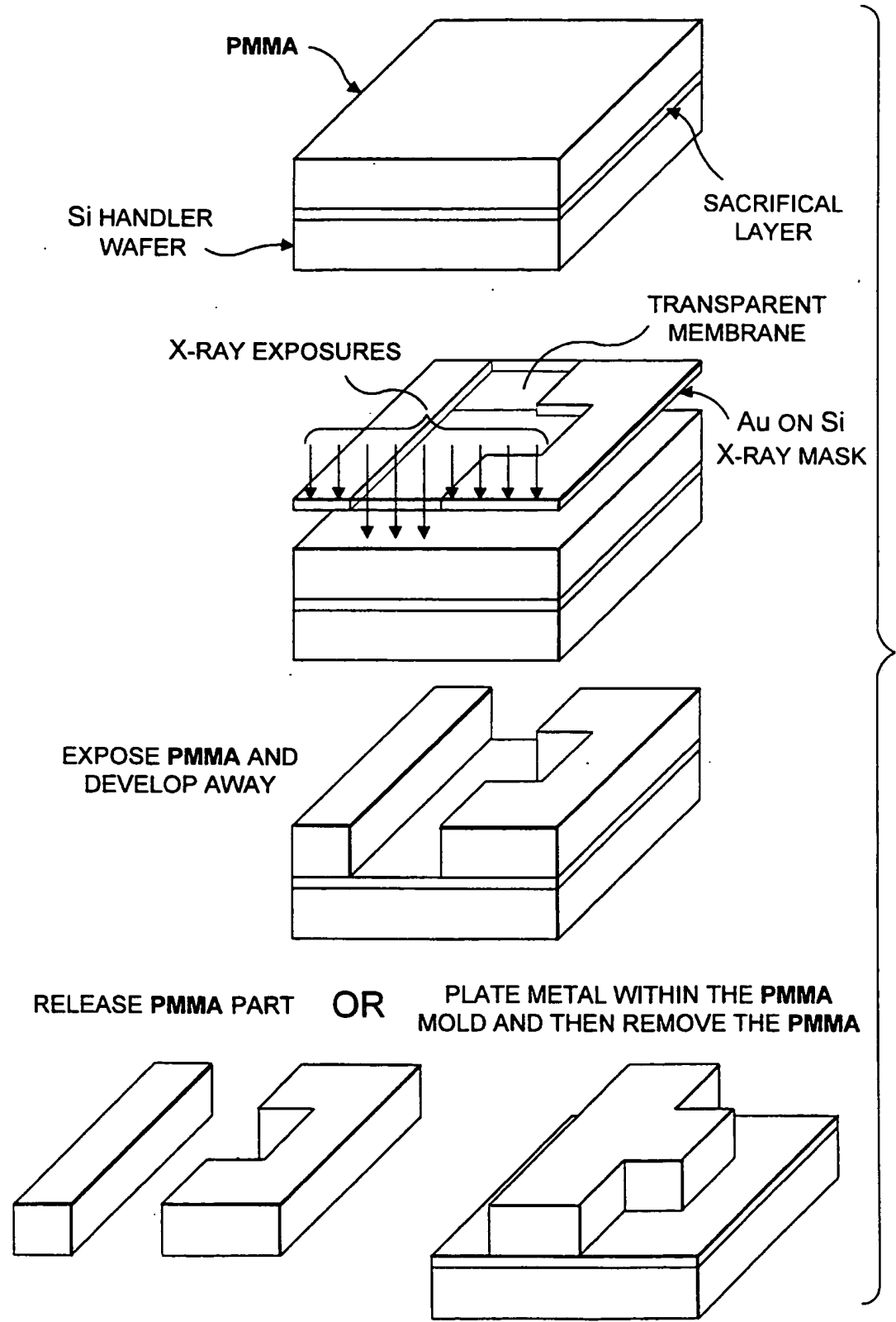


FIG. 2

3/9

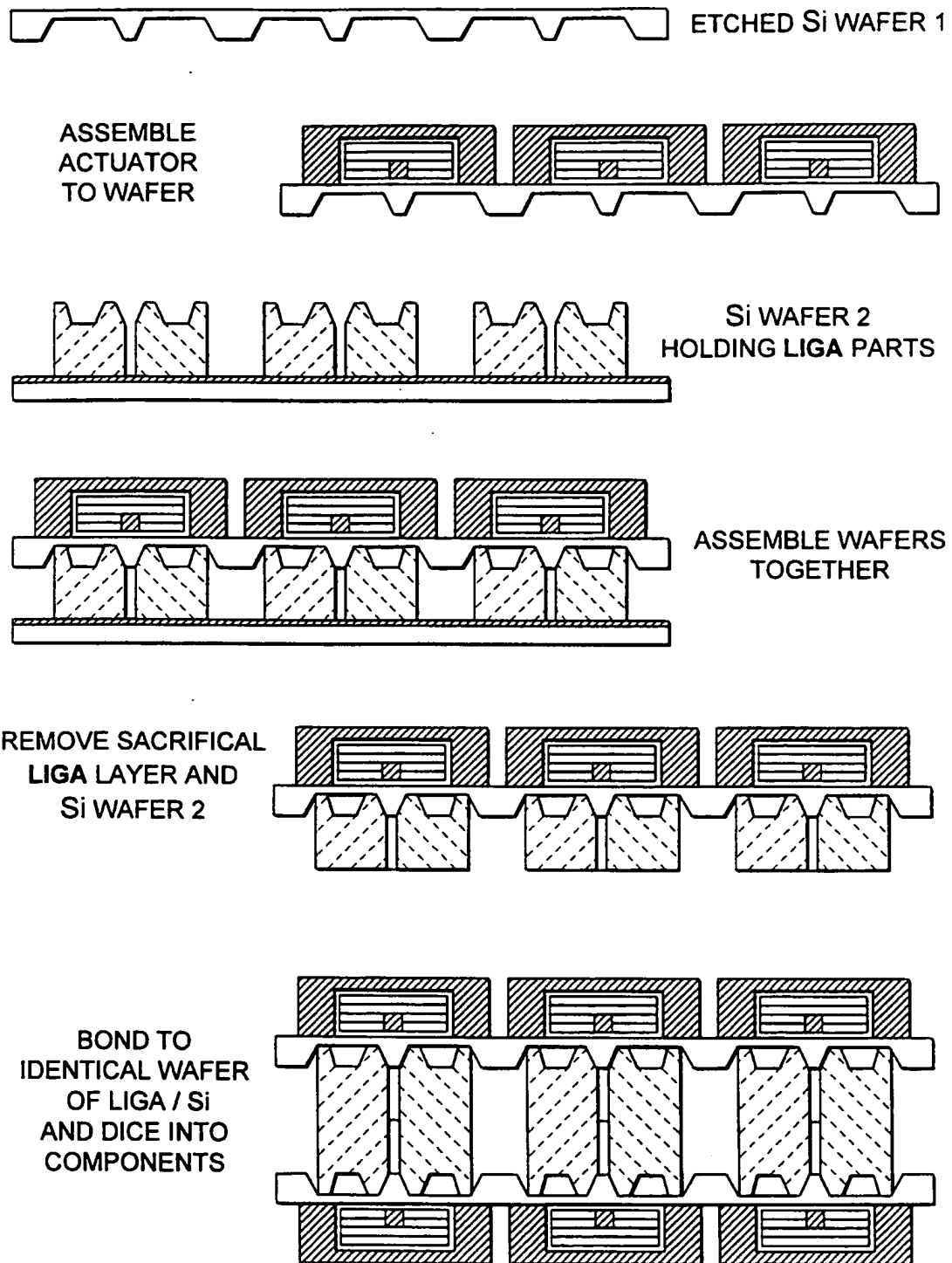


FIG. 3

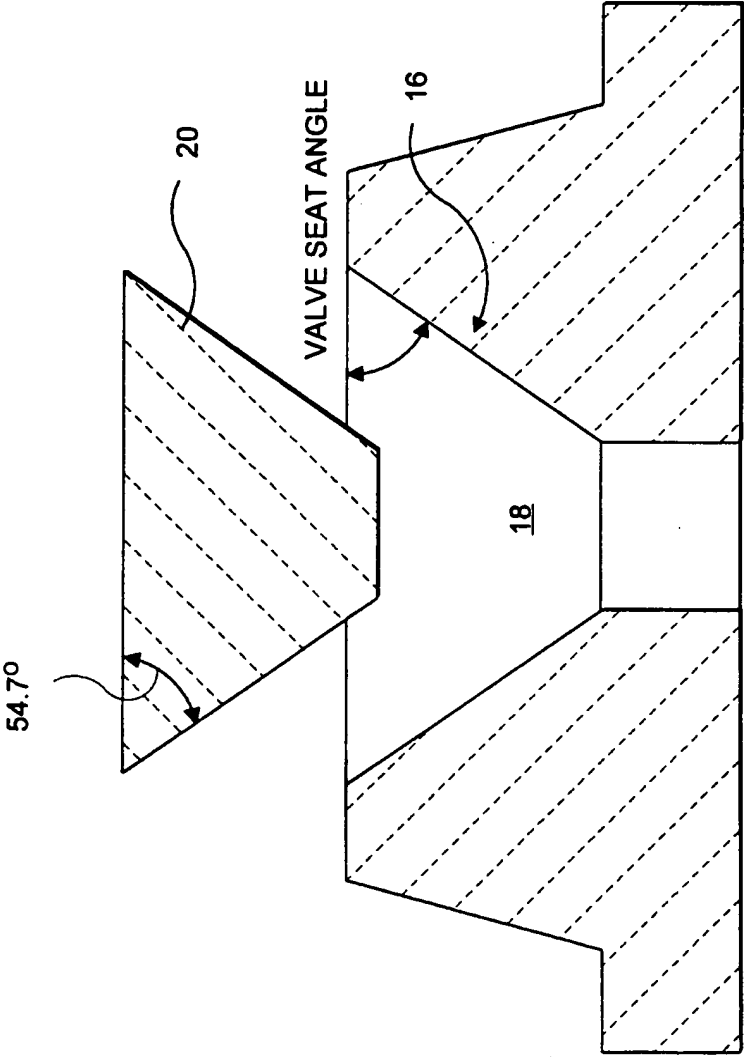


FIG. 4

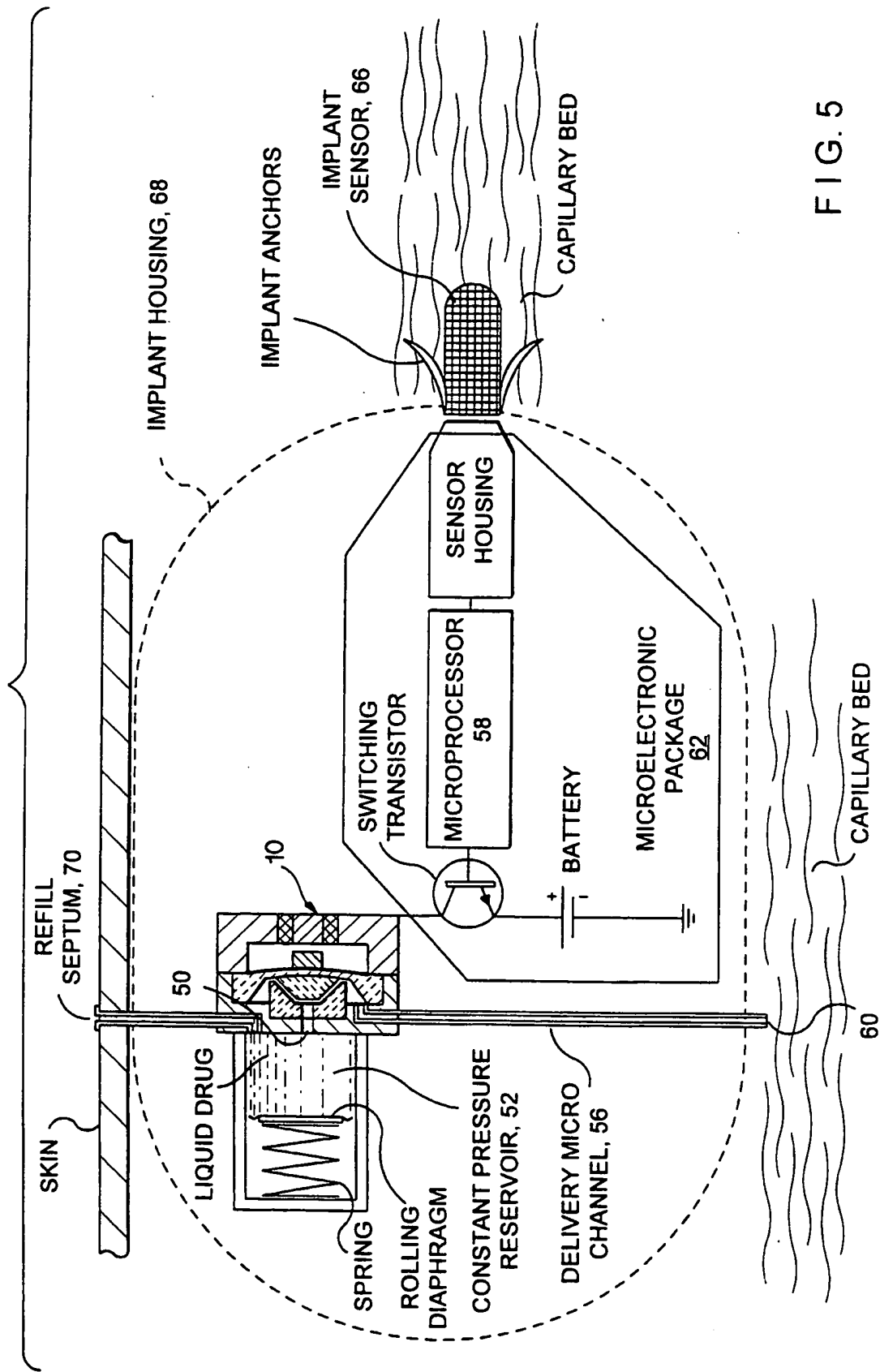


FIG. 5

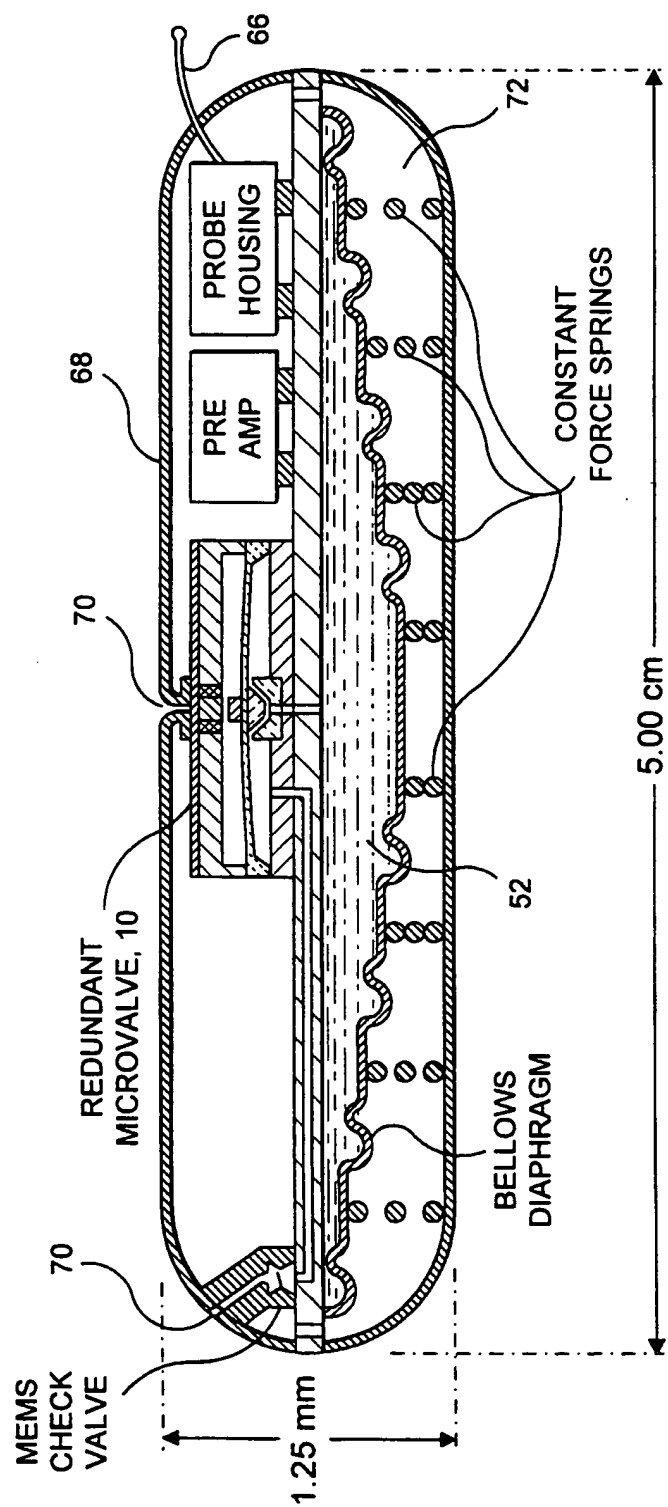


FIG. 6

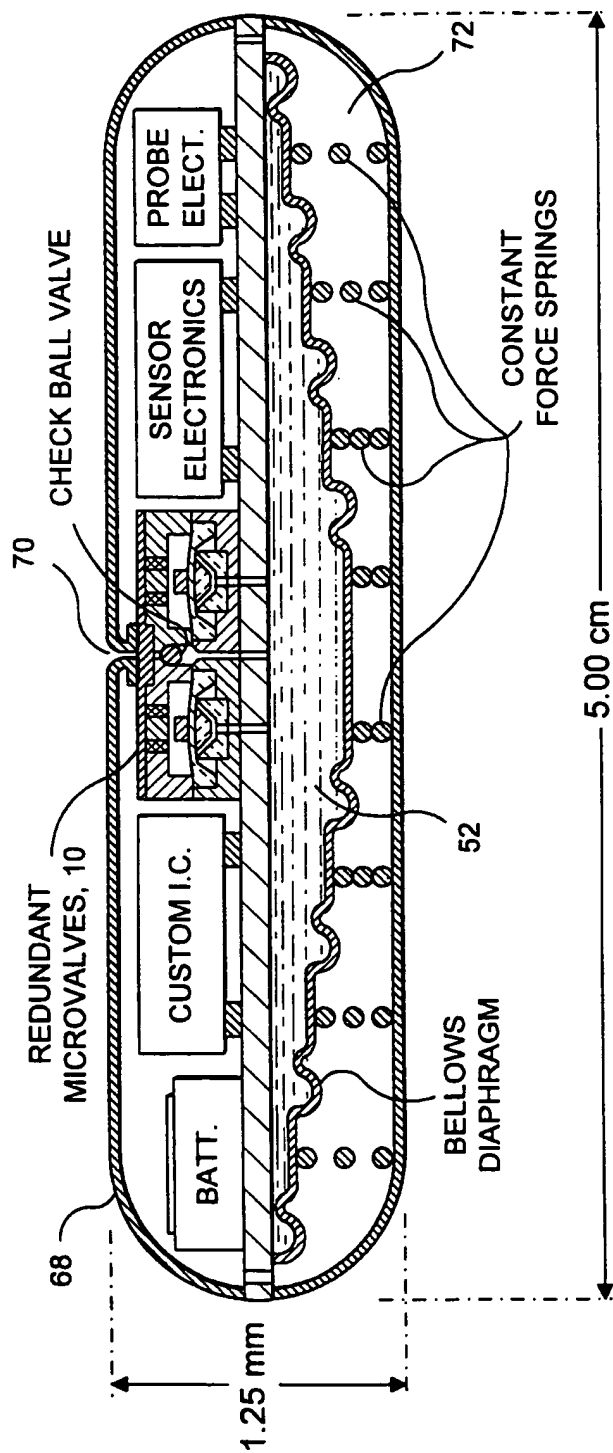


FIG. 7

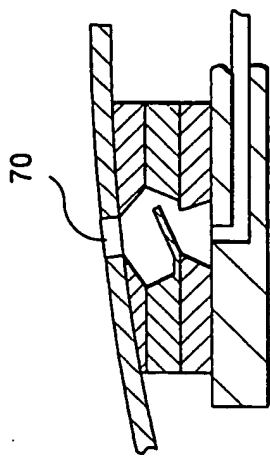


FIG. 9

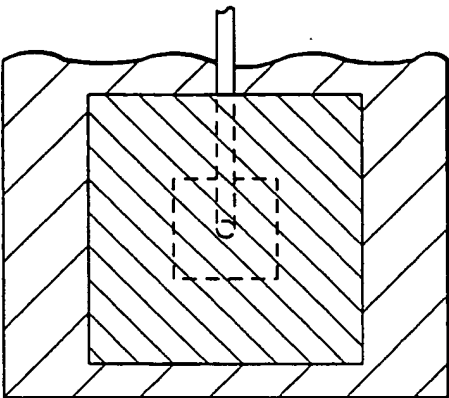


FIG. 10

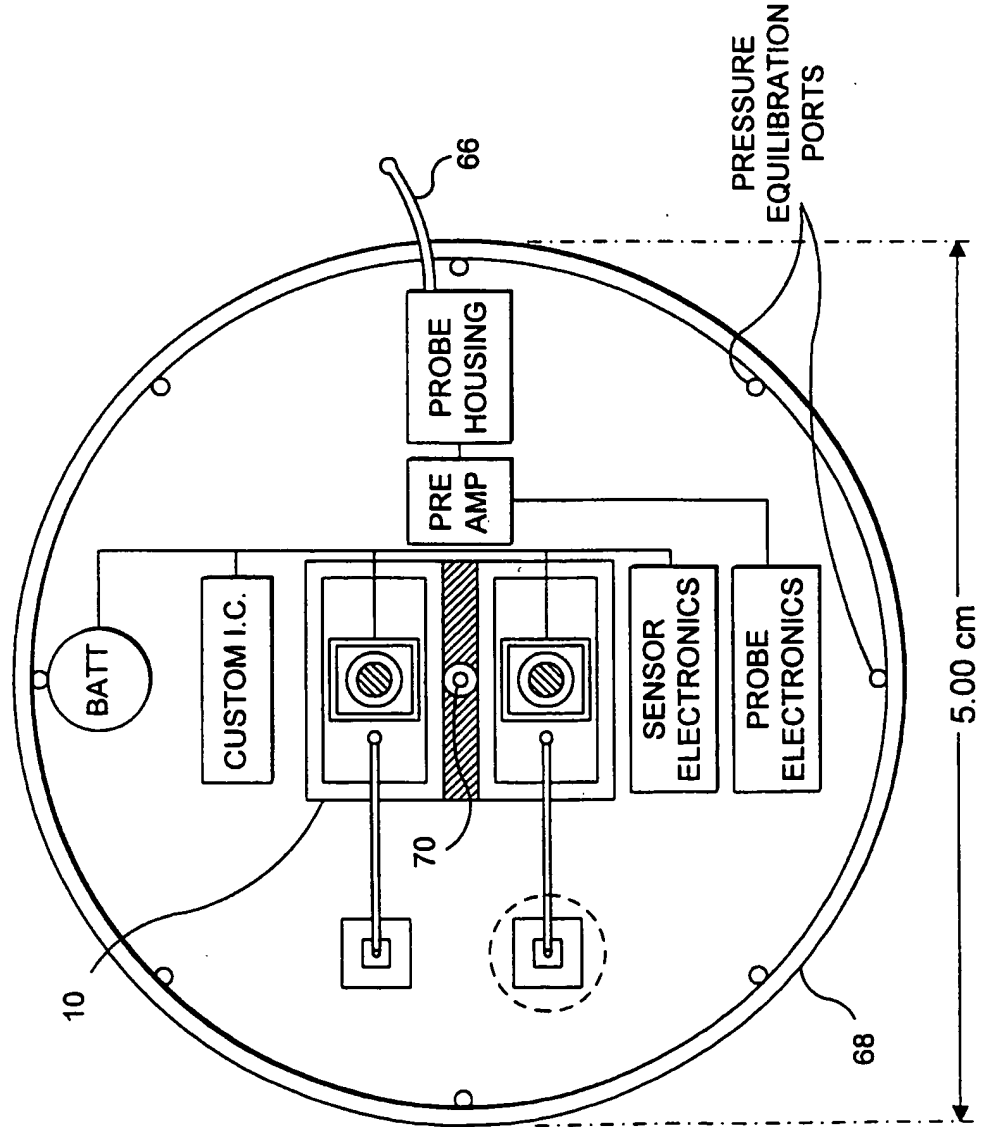


FIG. 8

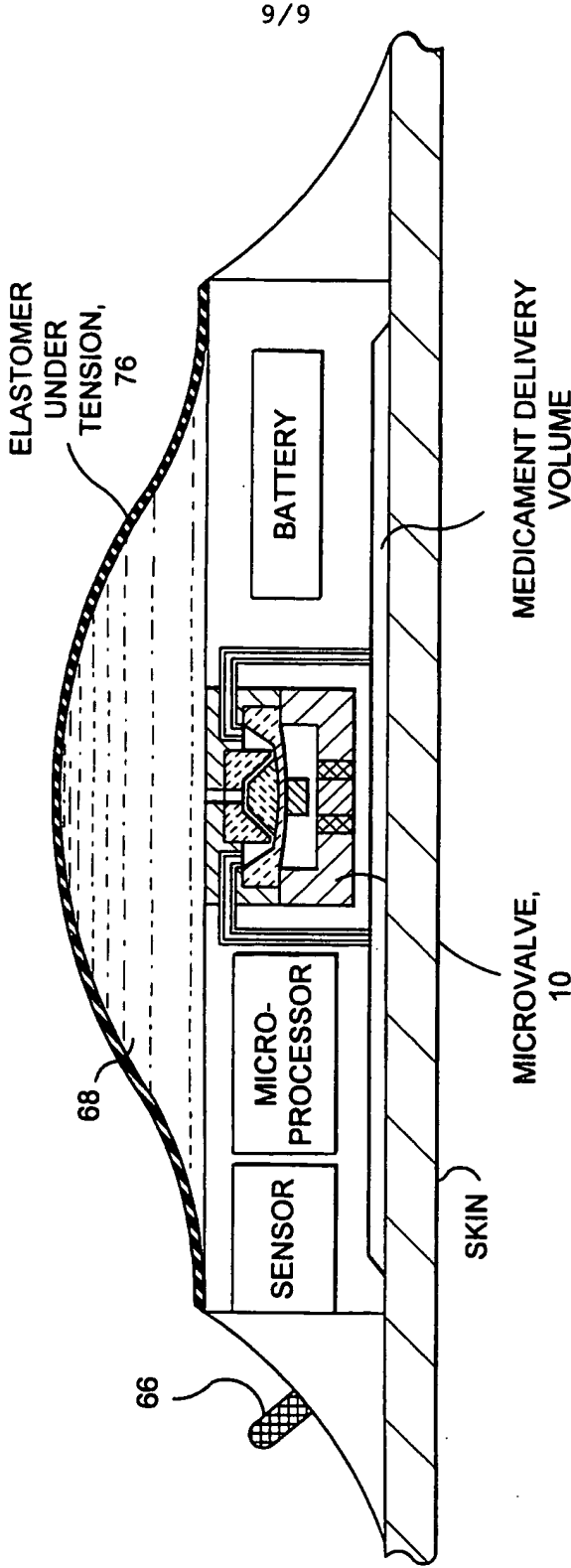


FIG. 11

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US98/17867

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/22; A61M 31/00; A61N1/30

US CL : 604/891.1, 20, 66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/20, 65-67, 93, 131, 245-247, 256, 890.1, 891.1, 892.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | US 4,443,218 A (DE CANT, JR. et al) 17 April 1984, entire document. | 1, 2, 4-7 |
| X | US 5,237,993 A (SKRABAL) 24 August 1993, entire document. | 1, 2, 4-7 |
| A | US 4,193,397 A (TUCKER et al) 18 March 1980, entire document. | 1, 2, 4-9 |

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| *E* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document member of the same patent family |
| *U* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

16 NOVEMBER 1998

Date of mailing of the international search report

24 DEC 1998

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